REMARKS

In response to the Office Action of April 19, 2004, claim 1 is hereby amended, claims 4-7, 9-10, 19 and 20 are canceled and claims 23-41 are added. Claims 1-8, 11-18 and 21 were rejected under 35 U.S.C. § 102(b), as being anticipated by Coolidge *et al.*, U.S. Pat. No. 5,221,736 and under 35 U.S.C. § 102(e), as being anticipated by Pieken *et al.*, U.S. Pat. No. 6,262,251. Claims 9, 10, 19 and 20 were objected to as being dependent on a rejected claim. Each rejection raised by the Examiner is discussed below.

Rejections under 35 U.S.C. § 102 (b)

The Examiner has rejected claims 1-8, 11-18 and 21 under 35 U.S.C. § 102(b) as being anticipated by Coolidge *et al.*, U.S. Pat. No. 5,221,736. The Examiner reasons that Coolidge *et al.* is directed to a method of purifying sequentially synthesized peptides and oligonucleotides by affinity techniques. Selected products are capped with an N-terminus capping agent for peptides or a 5'-terminus capping agent for oligonucleotides, and then bound with affinity agents that are selective for the corresponding capping agents. In one embodiment, an acrylic acid or related derivative is employed as the capping agent. The acid is coupled to the selected peptide or oligonucleotide through an acid chloride or anhydride reaction. Thereafter, the capped, selected products are removed by either a Diels-Alder reaction or by the addition of a radical initiating reagent.

The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); Alco Standard Corp. v. Tennessee Valley Auth., 1 USPQ2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991) (citations omitted).

As noted by the Examiner, Coolidge *et al.* teaches a method for the purification of sequentially synthesized oligonucleotides and peptides. In one embodiment, acrylic acid is employed as the capping agent. Thereafter, the capped compounds are removed by Diels-Alder reaction. The cycloaddition related methods described by Coolidge *et al.* are clearly limited to

the process of synthesizing the oligonucleotide via Solid Phase Oligonucleotide Synthesis (SPOS) and for the most part even further limited to the capping step of the SPOS process. As is well known in the art, the capping step is part of every elongation cycle of SPOS. It is positioned after the coupling step and/or after the subsequent oxidation step. During the coupling step the growing oligonucleotide chain is elongated by reaction with a phosphoramidite building block. The capping step typically comprises contacting the reaction mixture from the coupling/oxidation step with acetic anhydride in the presence of an auxiliary base in order to block all (usually 5'-) hydroxyl groups to which no phosphoramidite has been coupled during the preceding step. The rationale is to render unreacted hydroxyl groups inaccessible in subsequent coupling steps and in this way avoid formation of (n-1)-failure sequences that are difficult to remove from the final product.

In some embodiments Coolidge *et al.* use capping reagents with a Diels-Alder competent functionality enabling the removal of failure sequences by Diels-Alder mediated immobilization on the completion of the SPOS. This immobilization step entails the attachment of the different failure sequences that have formed during all cycles of the SPOS, resulting in a support carrying a number of different truncated oligomers. These immobilized oligomers represent a random collection of failure sequences rather than a defined product with a reproducible biological activity. Consequently, this embodiment of the Coolidge *et al.* method involves discarding these support-bound oligomers, followed by isolation of the remaining oligonucleotide having the desired sequence.

In further embodiments, Coolidge *et al.* introduce a Diels-Alder competent functionality in the last cycle of the SPOS procedure. In this case, the functionality is part of the 5'-protective group of the nucleotide building block that is incorporated into the oligonucleotide sequence as the last 5'-terminal nucleotide. After the completely assembled oligonucleotide is cleaved from the solid support, it is removed from the reaction mixture by trapping it on a support via the Diels-Alder reaction and finally releasing and isolating it by removal of the 5'-protective group. Thus, said 5'-protective group not only has to include the Diels-Alder competent functionality, but also has to possess the same or at least similar characteristics as the DMT group typically used in SPOS for 5'-protection. In particular, it has to be removable under mild conditions that do not interfere with any other functionalities of the oligonucleotide. Coolidge *et al.* do not at all

reduce this method to practice, nor do they teach how such a protective group should be devised, although sophisticated synthetic work would be required, if accomplishable at all.

Furthermore, in both of these Diels-Alder related methods suggested by Coolidge *et al.*, the removal of either the failure sequences or the desired final product via immobilization, are based on the introduction of a Diels-Alder competent functionality in the course of the SPOS. For immobilizing the failure sequences this functionality is introduced in the capping steps and for immobilizing the completely assembled oligonucleotide the functionality is introduced via the last coupling step of the SPOS. In general, the incorporation of a Diels-Alder competent functionality is always directly related to the process of assembling the desired oligonucleotide or oligopeptide.

In conclusion, Coolidge *et al.* do not teach or suggest the introduction of a Diels-Alder competent functionality to an oligonucleotide that is completely assembled and already has the desired sequence. They also do not teach or suggest the permanent immobilization of oligonucleotides in order to enable/facilitate subsequent procedures, such as hybridization based assays. Additionally, Coolidge *et al.* neither teach nor suggest the use of any cycloaddition reaction other than the Diels-Alder reaction using acrylic acid as the dienophile.

The present invention is drawn to a method for immobilizing a molecule on a support employing a cycloaddition reaction. Claim 1 has been amended to specify that the derivatization of the molecule with a functional group capable of undergoing a cycloaddition reaction is performed independent of all steps necessary for synthesizing the molecule. Support for this amendment is evident in the Specification, in that it is clear from the Specification that said derivatization is not included in any elongation cycle of the SPOS process. In particular, the derivatization is neither related to a capping step nor to a coupling step. In most cases, the derivatization is completely independent of the entire SPOS process. In some instances, however, the functional groups capable of undergoing cycloaddition are introduced to the already completed oligonucleotide sequence in an additional elongation cycle of the SPOS due to the ease of the respective synthesis route. But, in these cases the functionalization not part of any steps for assembling the desired oligonucleotide and is not achieved via a capping step or the step of coupling the final nucleotide building block which completes the synthesis of the intended oligonucleotide sequence. In short, Coolidge *et al.* apply immobilization by Diels-

Alder as a purification step in oligonucleotide and peptide synthesis in order to isolate the unbound final product. They introduce the appropriate functionalities via capping steps using corresponding capping reagents and chemistries that are limited in that they are orthogonal to the other blocking groups involved and do not interfere with the other steps of the SPOS reaction cycles. Or they introduce these functionalities as part of the 5'-protective group of the last nucleotide building block to be coupled in the final elongation cycle. In contrast, the present invention describes the synthesis of cycloaddition competent molecules, in particular biomolecules, and their conversion into immobilized formats, such as oligonucleotide arrays, which are useful e.g. for genotyping assays. The functionalization of the molecules is not part of any step for assembling the molecules, let alone restricted to the capping step or the final coupling step. For these reasons, Applicant maintains that claim 1, as amended, is not anticipated by the Coolidge *et al.* reference and respectfully requests that this rejection be withdrawn.

As noted above, new claims 23–41 have also been added. New claim 23 excludes the Diels-Alder reaction. Applicant maintains that independent claim 23 and claim 24 which depends from claim 23 are not anticipated by the Coolidge *et al.* reference, which as noted above only discloses the use of a Diels-Alder reaction.

New claim 25 is drawn to the method of the invention wherein the molecule being immobilized on the support is a diagnostic detector molecule. As defined in the Specification, "DDM's" include fluorescent, chemiluminescent, radioisotope and bioluminescent marker compounds; antibodies, biotin and metal chelates. (Specification, page 13, lines 14-16). As noted above, Coolidge *et al.* only teaches the immobilization of sequentially synthesized oligonucleotides and peptides. Since Coolidge *et al.* do not teach or suggest immobilization of DDM's independent claim 25 and claims 26-27 which depend from claim 25 are not anticipated by the Coolidge *et al.* reference. Applicant respectfully requests that this rejection be withdrawn.

New claims 28-31 are discussed below with respect to the objections to claims 9, 10, 19 and 20.

Finally, new claims 32-41 drawn to a method of synthesizing an array of molecules on a support using the method of this invention have been added. Support for the preparation of an array using the cycloaddition/bioconjugation method disclosed herein can be found in U.S. Pat.

No. 6,737,236 (the '236 patent). This application is a continuation in part of the '236 patent, which has been incorporated into the instant application by reference in its entirety. (Specification, page 4, lines 24-25). Example 19 (col. 56) of the '236 patent describes general method for conjugating 5'-diene modified oligonucleotide (col. 56, Scheme 29, lines 42-55) to a specific site on a wafer by reaction with a wafer which has been derivatized with a dienophile precursor. (col. 56, lines 60-62). In Example 19 of the '236 patent, the wafer is derivatized with a triazoline dione, which is a very reactive dienophile (col. 57, Scheme 30, lines 1-25) and the cycloaddition reaction is a Diels-Alder reaction. The method of the instant invention extends the method disclosed in Example 19 of the '236 patent to the preparation of an array of molecules using virtually any cycloaddition.

Rejection under 35 U.S.C. § 102(e)

The Examiner has rejected claims 1-8, 11-18 and 21 under 35 U.S.C. § 102(e) as being anticipated by Pieken *et al.*, U.S. Pat. No. 6,262,251 ('251 Patent). The '251 Patent has both a common assignee and common inventor with the instant application. With respect to the Section 102(e) rejection Applicant is submitting a Section 132 declaration executed by Wolfgang Pieken, the inventor in common with each of these cases. Applicant respectfully requests that this rejection be withdrawn.

Claim Objections

Claims 9, 10, 19 and 20 were objected to as being dependent on a rejected base claim. In response to this objection each of these claims has been redrafted as an independent claim, claims 28, 29, 30 and 31, respectively.

Applicant believes that the pending claims are now in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The

undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: September 20, 2004

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